American Journal of Pharmacy

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

DR. IVOR GRIFFITH RECEIVING
THE 1960 REMINGTON MEDAL

Since 1825 *December 1960*

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THE CHILLING TALE OF THE PHARMACIST WHOSE ASSETS GOT FROZEN

When the first bargain buy arrived, he made mental calculations and began thinking about Bermuda.

Fifty dozen at $1.40 each . . . I sell for $2.75 . . . take out 30 percent for overhead . . . enough left for plane fare . . .

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But, to his sorrow, most of the bargain merchandise stayed on his shelves, and he spent January wishing he could have a clearance sale like other stores.

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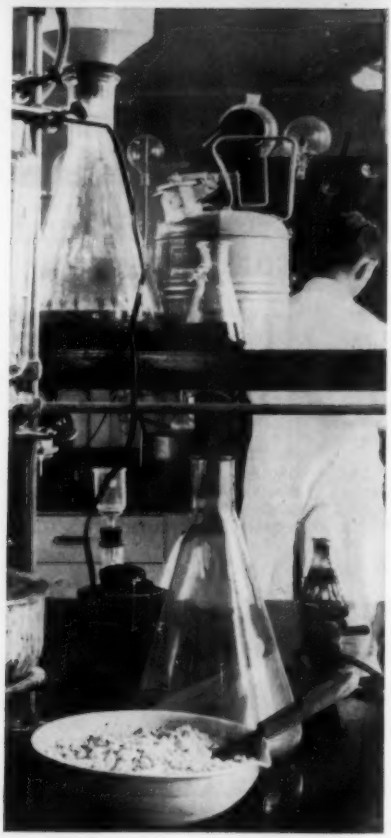

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AMERICAN JOURNAL OF PHARMACY

AND THE SCIENCES SUPPORTING PUBLIC HEALTH

Since 1825

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CONTENTS

OUR COVER

THE 1960 REMINGTON MEDALIST AND HIS CO-WORKERS *

By Louis Gershenfeld, D.Sc.**

TOASTMASTER Doctor Sica, Remington Medalist for 1960, Honored Guests, Members and Friends of the New York Branch of the American Pharmaceutical Association:

It has become my agreeable lot to be the voice of the members of the Faculty of the Philadelphia College of Pharmacy and Science and of other co-workers in the health sciences, who have been associated with the 1960 Medalist during the past several decades. In this capacity for the moment, I cannot help but think of the co-ed who accidentally dropped her expensive camera in the water of a swimming pool adjacent to the campus. She called to one of the professors nearby and asked him to kindly retrieve it. "Why was I chosen?" he asked. "Oh, you don't recognize me, professor" was the reply. "I am in one of your classes and, frankly, I know of no one who can go down deeper, stay down longer, and come up drier than you." Speaking for myself, the time allotted will not permit me to go down too deep, nor stay too long, and I will try not to come up too dry.

There are many descriptive words which can be used describing the Medalist's varied activities during his long, colorful, and productive career. Any one of these alone is enough to make up the life work of most individuals, but to find them all so capably expressed by one individual is extraordinary indeed. A well-known scientist, an inspiring teacher, educator, author, and editor; a capable leader and master executive; a warm friend; and one always cooperating with and solicitous of his co-workers. He is unique in his unselfish service and devotion. The extreme simplicity of his nature, his energy and courage even under adversity, and his boundless en-

* Delivered at a special meeting of the New York Branch, American Pharmaceutical Association, and Testimonial Dinner tendered Doctor Ivor Griffith, recipient of the 1960 Remington Honor Medal, at Hotel Roosevelt, New York City, December 7, 1960.

** Chairman of the Faculty Council and Director of the Department of Bacteriology, Philadelphia College of Pharmacy and Science.

thusiasm and zest for living have earned him universal respect and admiration. He has the capacity to raise men's hopes, strengthen their wills, and bring out the best that is within them. Perhaps the reason for the Medalist's influence on his co-workers can be summed up in the words of Emerson: "This is the key to the power of the greatest men—their spirit diffuses itself."

The pharmaceutical and allied scientific community in this great land of ours grew up during the period of the Medalist's active life. For more than fifty years, he has been associated with the Philadelphia College of Pharmacy and Science—as student, alumnus, President of its Alumni Association, instructor, professor, head of the Department of Pharmacy, dean, emeritus professor, editor of its *American Journal of Pharmacy and the Sciences Supporting Public Health*, the first recipient of the Alumni Award, and for the last twenty years as our Comrade-in-Chief, President of the College. He is the only individual in the one hundred forty years' existence of our College to occupy all of these stations. In associated fields in the health sciences, the 1960 Remington Medalist served in our city as Director of the Pharmaceutical and Clinical Laboratories at Stetson Hospital, as Research Director of the John B. Stetson Co. and also the McNeil Laboratories, as Professor and now Honorary Professor of Organic Chemistry at the Wagner Free Institute of Science, as a former member of the Pennsylvania State Department of Health and just recently appointed for the nineteenth year as Chairman of the State Advisory Committee on Laboratory Procedures, and also as a former Chairman of the Food and Drug Committee of the Philadelphia Department of Public Health. In his duties associated with the John B. Stetson Co., and later as Research Director of the Frank H. Lee Co., at Danbury, Conn., he was successful in replacing the toxic mercurials used in the industry by other more efficient chemicals, thus contributing to the health of the workers in the hat industry. Time is not available to do more than mention the services and his accomplishments as President of the Welsh Society and the St. David's Society as well as his activities in many communal, fraternal, and scientific organizations or to detail the many honors which have come to him. This, however, is worthy of note. After the award of the Remington Honor Medal later this evening, Dr. Griffith will be the only one to have received both the Procter and the Remington Medals, the highest awards in American and probably World Pharmacy.

His intimate friends and co-workers know him as IVOR, the

I standing for incomparable, informative, and inspiring

V standing for versatile, vigorous, and vitality

O standing for organizer, originality, and optimist

R standing for realist, reliable, and revered.

It is these intimate friends and co-workers who are delighted to be here this evening to extend congratulations and to which we add our tribute. With deep affection and admiration, we join in the universal prayer that our Medalist continue his dedicated life of fruitful service for many, many years to come.

May I conclude by saying we may well note that Doctor Griffith's spirit of self-sacrifice for the good of others is worthy of meditation in all our hearts, and his devotion to his friends and co-workers may well serve as an example for others to emulate?

EDITORIAL

THE EXPANSION OF DRUG CERTIFICATION BY THE FDA

ONE of the several recommendations made by the Committee appointed to study the Food and Drug Administration was that the present program involving the certification of certain antibiotics be expanded to include certification of all antimicrobial substances. Such a recommendation received the endorsement of Secretary Flemming but we sincerely hope that his successor, Mr. Ribicoff, will study this matter more carefully and come to a different conclusion.

The initial reason for the certification of antibiotics was a valid one but the validity of this requirement has long since ceased to exist and it remains with us largely we suspect because the Food and Drug Administration is loath to relinquish what has been a very important source of income for their laboratories outside of their appropriation from Congress.

In the early days, antibiotics were usually quite impure; they varied greatly from batch to batch and it was difficult, if not impossible, to write adequate standards whereby their purity and strength might readily be determined. Under these circumstances, it became necessary for the Food and Drug Administration to examine very carefully each batch of antibiotics produced as the only means available to give the public that protection for which it had the responsibility. Antibiotics today, however, have long since come of age. We look upon these substances now in the same way exactly as we consider hundreds of other potent, life-saving substances. Modern methods of protection and purification have resulted in the preparation of antibiotics which are almost essentially pure substances and, indeed, in most instances, they are recrystallized and possess a degree of purity of about the same order as any other fine chemical. Those responsible for the official compendia; namely, the *United States Pharmacopeia* and the *National Formulary*, prepare and publish very exact standards for these substances, as well as clearly defined procedures which make it possible to determine conformity to these standards. The point which we are making is that there is no real difference between an antibiotic and, shall we say, an alkaloid or glycoside. Each is a very potent and useful substance and one is no more life-saving than another, the determining factor in each case being the disease from which the patient suffers and the medicament

which is needed. Surely, digitalis or digitoxin is just as essential to the patient with congestive heart failure as is an antibiotic to a person suffering with some infection. It is our firm opinion that no clear case can be made for placing antibiotics in a special class and that they should not be so considered.

There are some who might argue that all drugs, regardless of category, should be subjected to precertification by the Food and Drug Administration before they can be sold. By no stretch of the imagination could this be done and, even if it were done, the increased cost—which, of course, would need to be passed to the ultimate consumer—would be staggering. In fiscal 1959, it is claimed, the certification of six antibiotics cost the drug industry 1.2 million dollars. One can only guess what the astronomical figure would be if all drugs were precertified. It has, furthermore, not been demonstrated that certification even of these is necessary. In fact, we suspect that the records would show the reverse to be true.

There are changes needed in the operations of the Food and Drug Administration and these have been well documented for a long time. There needs to be a better inspection of production and control facilities among drug manufacturers, and there needs to be greater effort expended in determining whether drugs shipped in interstate commerce meet the official requirements of the U. S. P. and N. F. These activities require and, in fact, demand greater financial support from Congress than the FDA has received to date. It is inherently wrong for manufacturers to be required to pay for having their drugs certified as to purity and potency and, indeed, it has been just this program which brought about one of the developments for which the Food and Drug Administration merited its most severe criticism.

We have in the United States an ideal system whereby the standards of purity and strength of all important drugs are established by recognized professional experts working in behalf of the *United States Pharmacopeia* and *National Formulary*. These same standards then are used by the Food and Drug Administration in determining whether drugs in interstate commerce are suitable for use. This system has proved workable and effective and it should not be abandoned in favor of some new system which would prove both exceedingly expensive and open to all sorts of abuses not in the ultimate interest of the industry, the government, or the public which both serve.

L. F. Tice

STABILITY PROBLEMS WITH SOME VITAMINS IN PHARMACEUTICALS * †

By Thomas J. Macek ††

Vitamin and vitamin-mineral compositions, unlike other physiologically-active materials, are prepared in dosage forms primarily as mixtures. Such mixtures represent one of the largest, economically-important groups of modern pharmaceutical products. Interactions between vitamins and between the vitamins and other components may be found in such products, however, even though the vitamins are stable by themselves.

The literature and some personal experiences are reviewed. The discussion first summarizes the important decomposition pathways for vitamin A, thiamine, riboflavin, ascorbic acid, vitamin B_{12}, and pantothenic acid. The manuscript then considers interactions between thiamine and pantothenic acid, thiamine and cyanocobalamin, thiamine and riboflavin, cyanocobalamin and ascorbic acid, niacinamide and ascorbic acid and cyanocobalamin with folic acid.

VITAMIN and vitamin-mineral compositions, unlike many other physiologically-active materials, are prepared in dosage forms primarily as mixtures. Such mixtures represent one of the largest, economically-important groups of modern pharmaceutical products. Not unexpectedly, however, these multi-component products exhibit numerous problems with stability even though most of the individual vitamins are stable and may be prepared into reasonably stable dosage forms by themselves. Furthermore, certain of the decomposition reactions in multivitamin systems are not yet fully understood. This

* Presented at the Second Annual National Industrial Pharmaceutical Research Conference, Land O'Lakes, Wisconsin, June 12-15, 1960.

† A contribution from the Merck Sharp & Dohme Research Laboratories, West Point, Pennsylvania.

†† Director, Pharmaceutical Research and Development, Merck Sharp & Dohme, West Point, Pennsylvania.

prevails despite considerable progress in the art of preparing formulations having sufficient balance in potency to permit wide-scale, commercial distribution. In recent times, however, even this has been questioned, as in Canada, leading to various proposals for labeling products with expiration datings.

Interaction of vitamins may be found in all conventional formulations, including dry-filled and oil-filled gelatin capsules, compressed tablets, as well as in liquid oral and liquid parenteral products. At times, even inert formulation additives and diluents may be involved, particularly as they alter pH, supply moisture, or introduce trace metals or other reactive contaminants.

From the point of view of formulation, certain interactions of vitamins are more important than others. These will be discussed. Some prominent incompatibilities between the vitamins and non-vitamin formulation additives will also be noted. A full review of the very large literature on vitamins, however, is beyond the scope of this paper.

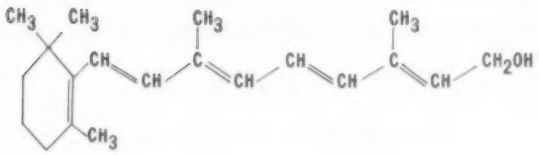
The more labile vitamin compounds are vitamin A, thiamine, riboflavin, ascorbic acid, vitamin B_{12}, and pantothenic acid. Discussion of the general problems of stability of each of these would seem worthwhile before proceeding with a consideration of some of the more specific interactions observed in product formulation.

Vitamin A—This compound occurs naturally in the animal organism as the free alcohol but predominantly in esterified form. For pharmaceutical use, it is today also prepared by synthesis. Esters such as the acetate and palmitate generally are preferred to the alcohol because of greater stability. The pure, crystalline acetate has been established as the international standard. Ethers have been made although some are biologically inactive. Vitamin A aldehyde possesses a biological potency equivalent to vitamin A alcohol, but is very unstable. Vitamin A acid has been obtained as a crystalline solid having about two-thirds of the activity of the alcohol. The properties of a number of derivatives are summarized in Table 1.

Vitamin A is sensitive to oxidation and readily undergoes autoxidation and polymerization. The oxidation is catalyzed by traces of metals, notably copper and iron, but the process is inhibited appreciably by the addition of antioxidants such as propyl gallate, hydroquinone, alpha-tocopherol and especially by combinations of

TABLE I

VITAMIN A_1 AND DERIVATIVES



	M.W.	M.P.	E 1% + 1 cm.	Biopotency I.U./Gm.
Alcohol	286.4	64°	1835	3.33×10^6
Aldehyde	284.4	68°	1510	3.3
Acid	300.4	180°	1600	2.2
ESTERS				
Acetate	328.5	57-8°	1550	2.91
Butyrate	356.5	---	1345	2.20
Laurate	468.7	---	1035	1.70
Palmitate	524.8	28-9°	975	1.60
Stearate	552.9	---	940	1.50
Benzoate	390.5	---	1240	1.80
Succinate	654.9	77-8°	1480	2.50
ETHERS				
Methyl	300.5	34-5°	1660	3.50
Phenyl	362.5	90-2°	1460	0.10

+ λMax. 324-28 millimicrons (ethanol)

these antioxidants. High potency oil solutions of vitamin A esters containing antioxidants are used in liquid formulations and soft gelatin capsules. The acetate coated with gelatin or a gelatin-starch composition to give a stable, dry form is widely employed in dry capsules and tablets.

Vitamin A dissolved in vegetable oil can be destroyed when the oil becomes rancid owing to the formation of peroxides. The amount of decomposition varies with the kind of oil or fatty acid ester present but may be inhibited by the addition of an antioxidant, as indicated in Table 2.

TABLE 2

LOSS AFTER 150 HOURS AERATION *

	No Antioxidant	*0.05% Propyl Gallate*
Peanut Oil	76%	31
Ethyl Oleate	74%	31
Ethyl Stearate	47%	31
Mineral Oil	72%	45
Mineral Oil Ethyl Oleate	79%	36
Mineral Oil Ethyl Stearate	46%	25
Mineral Oil Glyceryl Monolaurate	69%	13

* 4 ml./sec. dry air passed through 750 IU vitamin A in 25 ml. solvent at 28-9° C.

Ref.—*Chem. Abst.*, *44*, 4098 (1950).

Although thermal decomposition has been observed, vitamin A is quite stable when heated at moderate temperatures in an inert atmosphere in the dark. It is easily destroyed upon exposure to ultraviolet light, however, losing the typical absorption band at 325-328 millimicrons, forming biologically inactive products.

Vitamin A contains a series of five conjugated double bonds, four of which are in the side chain. Addition reactions, therefore, can occur with substances like bisulfite and certain solvents. With such high degree of unsaturation, numerous *cis-trans* isomers also

are possible (1). Natural vitamin A is all *trans*. This spatial arrangement is the most active biologically. The conversion of some of the double bonds into *cis* structures may decrease biological potency very appreciably although chemical assay may not be affected significantly. The properties of some geometric isomers are summarized in Table 3.

TABLE 3

PROPERTIES OF GEOMETRIC ISOMERS OF VITAMIN A PALMITATE

Isomer	*USP XV Potency u/Gm.*	*Biopotency u/Gm.*	*Biopotency*
All-trans	1.8×10^6	1.8×10^6	100
2-Mono-*cis*	1.30	1.37	105
6-Mono-*cis*	1.26	0.41	33
2,6-di-*cis*	1.32	0.41	31

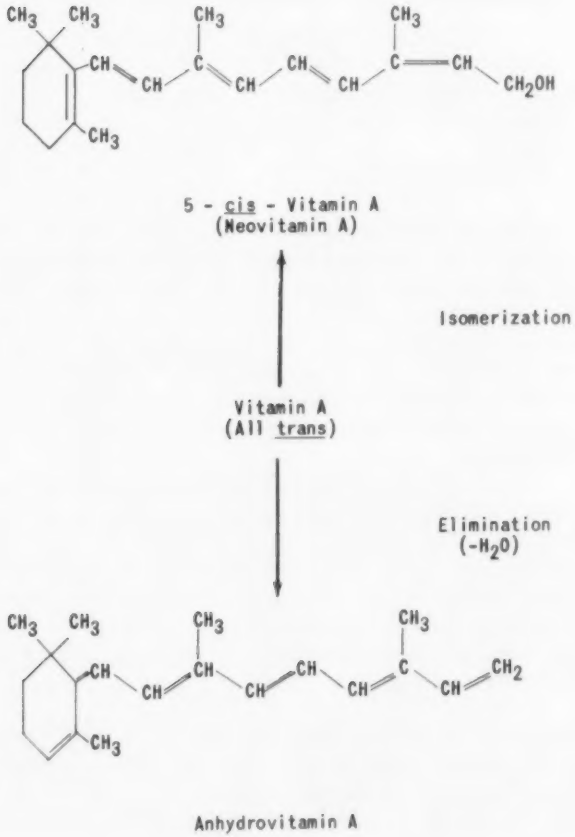
Such changes have been reported recently to occur to the extent of about 20% of the vitamin A content in aqueous multivitamin dispersions and were readily detected by the reaction with maleic anhydride. The all *trans* and 6-mono-*cis* forms react rapidly to give an adduct which fails to give the typical blue color assay with antimony trichloride. The 2-mono-*cis* and 2-6-di-*cis* forms react slowly with maleic anhydride and thus can be distinguished from the more reactive forms. Infrared studies have been employed to support these findings.

Mineral acids destroy vitamin A and its geometric isomers and form anhydrovitamin A, a hydrocarbon practically devoid of biological activity. This decomposition involving the loss of a mole of water, as shown in Figure 1, was first obtained by the action of hydrogen chloride in ethanol (2). The kinetics of the reaction were studied more recently by Higuchi and Reinstein (3) who reported a significant rate when vitamin A acetate was dissolved in alcoholic or hydroalcoholic solutions.

Thiamine—Thiamine is found naturally as the free compound, as salts, as protein complexes, and as the ester with pyrophosphoric acid (cocarboxylase). Thiamine Hydrochloride U. S. P. is commercially synthesized as thiamine chloride hydrochloride and crys-

tallizes from aqueous-alcoholic solutions as the hemihydrate, which melts with decomposition at 248-250°C. The molar proportion of water is not constant during storage and may vary depending upon humidity conditions. A moisture content not exceeding 5% is permitted by the U. S. P.

FIGURE I



In spite of its variable moisture, crystalline thiamine hydrochloride as a solid is stable for extended periods at room temperature and at elevated temperatures even in contact with air. Aqueous solutions of thiamine hydrochloride in the pH range 2.5-4.5 are stable for a considerable time.

Thiamine mononitrate, which crystallizes readily from water, is an anhydrous, non-hygroscopic form of the vitamin. It is soluble in water to the extent of 2.7 Gm. per 100 Gm. of water; the pH of such a solution is 6.8-7.1. Addition of a strong acid, e.g., HCl or nitric acid, to solutions of thiamine mononitrate increases solubility by virtue of the ionic equilibria involved. The addition of HCl to maintain a pH of 4, for example, results in concentrations of 18.5 Gm. thiamine mononitrate per 100 ml. at room temperature. The addition of a strong acid results in neutralization of the free amino group, the acidic pK of which is known to be 4.8.

Thiamine mononitrate does not deliquesce even on exposure to 90% relative humidity, differing markedly in this respect from thiamine hydrochloride and, therefore, is a more stable form of thiamine, particularly for dry or oil-based pharmaceutical preparations.

Solutions of thiamine at pH 3.5 can be heated at 120°C. without significant decomposition. The molecule decomposes appreciably above pH 5 and is extremely sensitive to heat in the neutral and alkaline pH range. Decomposition also occurs quite rapidly when alkaline solutions are merely stored at room temperature. There is increasing evidence that decomposition by hydrolysis may be a complex process yielding a number of products, the pyrimidine and thiazole moieties among them. Neither of these is biologically active.

In solution, pH appears to be the chief factor in the hydrolytic decomposition of thiamine although the literature contains numerous reports attributing stabilization and decomposition, both, to specific ions.

Thiamine is sensitive to both oxidation and reduction. Even mild conditions, such as storage of an alcoholic solution at room temperature for a long period of time, produce thiochrome by oxidation. This change occurs more rapidly as pH approaches 7. Since thiochrome possesses an intense blue fluorescence, it serves as a basis for assay following chemical oxidation of thiamine with alkaline potassium ferricyanide. In alkaline solutions, thiochrome is sensitive to light and the fluorescence disappears irreversibly. Thiamine can

be oxidized to a disulfide under physiological conditions at pH 7.5 with hydrogen peroxide or with oxygen. The same oxidation can be brought about in alkaline solution with iodine. The disulfide is fully active biologically. Mild reduction of thiamine with sodium hydrosulfide causes addition of a mole of hydrogen in the pyrimidine ring with almost complete loss of vitamin activity. Sodium sulfite, on the other hand, even at room temperature causes the so-called "sulfite cleavage" of the thiazole and pyrimidine portions, with nucleophilic addition of the sulfite to form an insoluble, biologically inert amino sulfonic acid.

For a long time, the industry was plagued by formation of trace, feather-like precipitates and discoloration in parenteral solutions of thiamine, particularly when exposed to light or heat. This problem today has largely been eliminated by the production of thiamine which is virtually metal-free, by proper choice of container components and by the discovery of numerous suitable stabilizers especially such compounds as monothioglycerol and thiosorbitol, some of which are covered by patents (4).

Riboflavin—Although widely distributed in nature, practically all of the riboflavin used in pharmaceuticals is prepared synthetically. The pure crystalline compound is only slightly soluble in water (12 mg. in 100 ml. at 27.5°C.). Because of its limited solubility and the desire to obtain more concentrated pharmaceutical solutions, riboflavin often has been combined with other compounds capable of increasing its solubility. These include N-methylacetamide, l-tyrosine amide, tryptophan, sodium acetyl tryptophan, urea, niacinamide, urethane, veratryl alcohol, gallic acid, salts of boric acid, propylene glycol, benzyl alcohol, and sodium 3-hydroxy-2-naphthoate. Most of these solubilizers have been described in patents. The most useful for pharmaceuticals probably are propylene glycol and niacinamide. At pH 5, riboflavin solubility increases approximately 250 times when niacinamide concentration is increased from 5 to 50 per cent. A super-saturated solution of riboflavin alone or with added solubilizer may be stable physically, often requiring days to crystallize. Some crystalline forms of riboflavin incidentally are alleged to be more rapidly soluble in water than others. Riboflavin also can be fused with solubilizing compounds such as urea, urethane, or niacinamide to give products which yield aqueous solutions up to 6% riboflavin concentration (5).

Water-soluble chemical derivatives include esters with succinic, citric, and other organic acids. However, not all of these are fully active biologically. On the other hand, the 5′-phosphoric acid ester is quite soluble as the sodium salt, is fully active biologically, and is an item of commerce. It possesses the incompatibilities of the phosphate ion, however, precipitating with calcium, with iron and other cations.

Crystalline riboflavin is stable at ordinary temperatures but exposure to light slowly destroys vitamin activity. In solution, stability of riboflavin is influenced largely by pH. Acid or even neutral aqueous solutions are stable to heat if protected from light and can be sterilized by autoclaving. Alkali decomposes riboflavin rapidly.

The rate of destruction by light becomes greater with increasing temperature and pH. Photolysis of riboflavin in neutral solution in the absence of oxygen causes disappearance of the color with the formation of deutero-leuco-riboflavin. This compound can be dehydrogenated by oxygen. Alkali subsequently converts the dehydrogenated compound to lumiflavin. Photolysis in alkaline solution also produces lumiflavin, whereas photolysis in acid or neutral solution produces lumichrome, an intensely fluorescent compound.

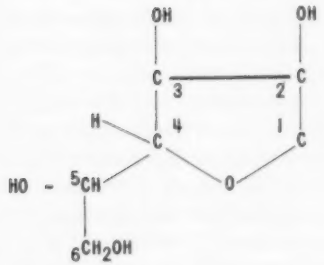
On reduction even with such mild agents as sodium thiosulfate, riboflavin readily takes up two hydrogen atoms. The dihydrocompound is colorless, shows no fluorescence, and is called leucoriboflavin. It is readily oxidized to riboflavin by air. Actually, three crystalline compounds can be obtained by stepwise reduction or hydrogenation of riboflavin, but these are of little consequence in pharmaceuticals.

Ascorbic Acid—l-Ascorbic Acid, a white crystalline optically-active solid, which melts with decomposition at 190-2°C., is a strong monobasic acid. It liberates carbon dioxide from carbonates and bicarbonates, and forms well-defined salts with cations such as sodium, potassium, calcium, and magnesium.

The outstanding feature of the structure is the presence of an α-keto-diol system involving carbons 1, 2 and 3 as shown in Figure 2. This portion of the molecule is responsible for the characteristic ultraviolet absorption, for the high acidity of the compound, and also for the well-known reducing properties of l-ascorbic acid.

FIGURE 2

ASCORBIC ACID



In solution at pH 2, there is an intense band of absorption in the ultraviolet with a maximum at 244 millimicrons and an extinction coefficient ($A\ \frac{1\%}{1\ cm.}$) of approximately 500. The absorption changes gradually as pH increases above pH 2. At pH 6 to pH 10, the solutions have a maximum at 266 millimicrons; more strongly alkaline solutions have a maximum at approximately 294 millimicrons.

A 1% solution of ascorbic acid has a pH approximately 2.5. Titration of this solution to pH 8 requires one equivalent of alkali. Although both hydroxyls of the ene-diol system are acidic, the first dissociation constant ($pK_1 = 4.1$) is associated with the hydroxyl at carbon 3. The second dissociation constant ($pK_2 = 11.6$) is associated with the hydroxyl at carbon 2.

Like all α-keto-ene-diols, l-ascorbic acid is a powerful reducing agent in acid and neutral solutions. It reduces Fehling's solution and ammoniacal silver nitrate, and reacts with iodine and other halogens and with dichlorophenol-indolphenol which is employed in its analysis. It also possesses chemical properties of a typical carbohydrate molecule, forming a bisphenylhydrazone with two moles of phenylhydrazine. The lactone portion of the molecule is remarkably resistant to hydrolysis. The principal decomposition of ascorbic acid, therefore, is oxidation, to which it is very sensitive, especially in aqueous

solution. The rate of oxidation increases in the presence of metals, especially copper or iron.

The first oxidation product of ascorbic acid is dehydroascorbic acid. This reaction is reversible and dehydroascorbic acid is reduced to ascorbic with hydrogen sulfide or HI. 1-Dehydroascorbic acid possesses the full biological activity of 1-ascorbic acid and, indeed, some of the naturally-occurring vitamin exists in the oxidized form. Further oxidation of 1-dehydroascorbic acid, however, involves extensive degradation to oxalic acid and 1-threonic acid and loss of activity. This decomposition is accelerated first by air and then by alkali. Neutral solutions of sodium ascorbate thus can be made in the absence of air which retain potency for long periods of time. Oxidation of ascorbic acid in vehicles such as glycerin, propylene glycol, sorbitol, or concentrated sugar solutions is low as shown by the data in Table 4. Stability of 1-ascorbic acid improves in aqueous

TABLE 4

ASCORBIC ACID

STABILITY IN VARIOUS VEHICLES

	Conc. = 100 mg./ml.			
	Water	*Syrup USP*	*90% Glycerin*	*Propylene Glycol*
Initial	100.0%	100.0%	100.0%	100.0%
RT-1 month	92.3%	98.0%	98.5%	97.0%
RT-3 months	79.0%	95.8%	97.0%	93.5%
RT-6 months	58.0%	86.5%	90.8%	85.7%
RT-12 months	34.7%	80.3%	89.0%	82.0%

	Conc. = 5 mg./ml.			
	Water	*Corn Syrup*	*Sorbitol*	*3% Methocel*
Initial	100.0%	100.0%	100.0%	100.0%
RT-1 month	90.0%	96.5%	99.0%	76.0%
RT-3 months	74.5%	92.0%	99.0%	39.5%
RT-6 months	40.5%	90.0%	96.0%	——
RT-12 months	——	76.0%	89.0%	——

Data from Bandelin & Tuschhoff, *J. A. Ph. A. 44*, 241 (1955).

solution with increasing concentrations of sodium chloride as shown in Table 5. The improvement in stability in these vehicles generally is associated with a lower concentration of dissolved oxygen in the vehicle. Addition of gums merely to increase viscosity of aqueous solutions is insufficient to exert an equivalent stabilizing effect.

TABLE 5

ASCORBIC ACID

STABILITY IN SALT SOLUTION

	Conc. = 1 mg./ml.—% Retained			
	Water	*1% NaCl*	*2% NaCl*	*5% NaCl*
6 Hours	77%	97%	100%	98%
24 Hours	55%	87%	97%	99%
3 Days	43%	63%	88%	99%
5 Days	5%	16%	65%	91%
7 Days	——	——	52%	93%
9 Days	——	——	39%	86%

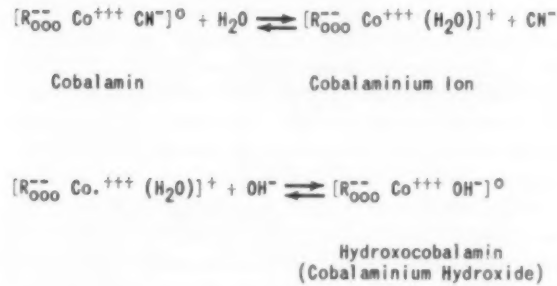
Vitamin B_{12}—Cyanocobalamin, the red crystalline form of vitamin B_{12}, was first isolated in pure state in 1948. In aqueous solution, this compound has a characteristic absorption spectrum with peaks at 278, 361, and 550 millimicrons. The spectrum is not markedly affected by small changes in pH.

Early investigations of structure revealed the presence of cobalt, phosphorus, and the cyano group. Potentiometric titration showed cyanocobalamin to be a polyacidic base containing six weakly basic groups. Further studies yielded evidence of a complex organic moiety which could be degraded to yield 5,6-dimethylbenzimidazoles and ribazoles, the ribofuranisido substituents of the former.

But despite its large organic molecular composition, cyanocobalamin essentially is a coordination compound of cobalt. Its chemistry and stability are best viewed in terms of the properties of this inorganic coordination complex. The cyano group, though very weakly ionized, is replaceable by other ions or molecules. The number of B_{12} modifications is limited only by the number of ions or molecules which can replace cyanide in the cobalt coordination complex. In the formation of vitamin B_{12a}, or hydroxocobalamin, the

cyanide ion is liberated and replaced by a hydroxo group. The cyano group may also be replaced by chloride, nitrate, acetate, and other anions to form the respective B_{12} anologs. Some of the latter are almost completely ionized. The general equilibrium for these transformations is represented in Figure 3.

FIGURE 3



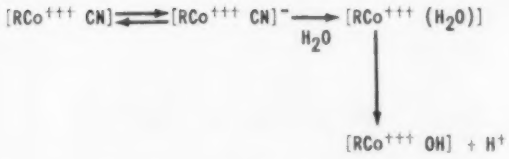
Symbols

- = negative charges
o = electron pairs

} - To satisfy the remaining coordination bonds.

Aqueous solutions of cyanocobalamin are most stable in the pH range of 4 to 7 at normal temperatures. Exposure to sunlight brings about loss of microbial activity. Autoclaving at pH 4.5 causes a slight decomposition but is probably of no consequence in pharmaceuticals. The presence of reducing agents, however, even in trace quantities, frequently introduced by way of formulation additives, can markedly influence potency as a result of decomposition of the reduced form to irreversible oxidation products. This is shown diagrammatically in Figure 4.

FIGURE 4



The outstanding incompatibility of cyanocobalamin, of course, is that with ascorbic acid. Decomposition products of thiamine, ferrous salts, sodium bisulfite, reducing sugars, and some flavors are equally destructive, however. Some of these will be considered presently.

Pantothenic Acid—d-Pantothenic acid itself is a yellow viscous oil and not used in pharmacy. It forms a crystalline water-soluble calcium salt, however, which is widely employed. The alcohol analog of pantothenic acid also is available in two forms. d-Pantothenyl alcohol is a viscous, colorless liquid and dl-Pantothenyl alcohol, a crystalline solid. Both forms are soluble in water and alcohol but not in oil. The dl-form is half as active biologically.

All forms of this vitamin are sensitive toward acids and bases, and to heat. The range of greatest stability is pH 4 to 7 with optimum stability at pH 6. Hydrolysis occurs at the amide linkage between the lactone and the β-alanine moieties and proceeds at an increasing rate as the pH varies from the optimum. The compound has high structural specificity so that hydrolysis is accompanied by loss of biological activity.

Thiamine and Pantothenic Acid—The kinetics of the hydrolysis of thiamine and pantothenate in acid solution was reported in 1944 by Frost and McIntire (6). The hydrolysis of pantothenate is a first-order reaction with respect to pantothenate concentration. The decomposition of thiamine, on the other hand, is much more complicated yielding several decomposition products as pH varies as shown by the paper chromatograms of Busse *et al.* (7).

The opposing stability relationships between thiamine and pantothenate as regards pH present practical difficulties in formulation, especially of liquid multivitamin products. To achieve optimum stability of thiamine, riboflavin, ascorbate, pyridoxine, and even of cyanocobalamin, multivitamin liquids usually are prepared at about pH 4. Under these circumstances, pantothenate is rapidly decomposed, potency often falling below label claim on storage of products even with the addition of large manufacturing overages.

The development of pantothenyl alcohol as a more stable analog of pantothenic acid for use in liquids aided in the stability problem. The rate of decomposition of pantothenyl alcohol was significantly less than pantothenate at pH 4 in both pure aqueous solution and in liquid compositions with other vitamins. In the more stable pH range of 6 to 8, however, the rates of hydrolysis of pantothenyl alcohol and calcium pantothenate were essentially the same (8).

The stability of the amide linkage in pantothenic acid to hydrolysis is influenced by the polarity of the terminal groupings on the molecule. The hydroxyl of pantothenyl alcohol is less polar than the terminal carboxyl of pantothenic acid. The inductive effect of the terminal carboxyl group increases the positive charge on the nitrogen and weakens the resonance of the amide. This is especially noted in mild acid solution. Weakening of the amide resonance favors hydrolysis (9).

In dry B complex mixtures, it has sometimes been the practice to add an acidic substance, such as tartaric acid, to lower pH and aid in the stability of thiamine HCl. Such a practice obviously is unfavorable to the stability of calcium pantothenate. When thiamine mononitrate is employed, the addition of an acidic stabilizer becomes unnecessary (10). Thiamine mononitrate, therefore, is much more compatible with calcium pantothenate in dry mixtures intended for use in capsules and tablets. Data showing differences in stability are shown in Table 6.

TABLE 6

DRY-FILLED B VITAMIN CAPSULES

	A	*B*	*C*
	Thiamine (3 mg./Capsule)		
Initial	100%	100%	100%
1 mo.-RT	62%	95%	100%
6 mo.-RT	17%	93%	100%
1 mo.-40°	32%	97%	95%
3 mo.-40°	21%	95%	97%
	Calcium Pantothenate (10 mg./Capsule)		
Initial	100%	100%	100%
1 mo.-RT	100%	92%	100%
6 mo.-RT	100%	65%	100%
1 mo.-40°	100%	62%	99%
3 mo.-40°	100%	16%	96%

A—Thiamine HCl, no tartaric acid.
B—Thiamine HCl with tartaric acid.
C—Thiamine Mononitrate, no tartaric acid.

In oil suspension compositions such as used in filling soft gelatin capsules, the stability of calcium pantothenate is improved when dibasic magnesium phosphate is added as a stabilizing component (11).

Thiamine and Cyanocobalamin—In one of the first published reports on stability studies with cyanocobalamin, Macek and Feller (12) observed a loss of 16% of cyanocobalamin (C = 15 mg./ml.) upon autoclaving an acetate buffered solution at pH 4 containing a large excess of thiamine hydrochloride (C = 100 mg./ml.). However, negligible loss of cyanocobalamin was observed when this same solution was stored at room temperature for a period of one year. It was concluded that there was no incompatibility between thiamine and cyanocobalamin.

Shortly thereafter, Blitz *et al.* (13) reported that cyanocobalamin was not stable in a B-complex parenteral solution at pH 4.25 containing both thiamine and niacinamide among its constituents. The large losses of cyanocobalamin observed by these workers could not be reproduced in subsequent experiments by the earlier workers. The B vitamin solutions were prepared at pH 3.0 and 4.5 and were steri-

lized without heat. They were stable even after prolonged storage (14). The discrepancy between the two studies was resolved, however, when it was realized that Blitz *et al.* employed concentrations of both thiamine and niacinamide that were substantially greater. Furthermore, the decomposition was easily accelerated by heat, or by the presence of thiamine decomposition products, notably the thiazole moiety, which functioned as a reducing agent for cyanocobalamin (15). The pyrimidine moiety had no effect on cyanocobalamin stability, nor did thiochrome (16).

More recent studies by Indian workers (17, 18) have confirmed these findings but have also proposed that the deterioration could be prevented by the use of iron salts. These studies indicated that the same iodine-titratable reducing substances were formed by the thermal decomposition of thiamine at pH 4.0-4.5 in the presence of niacinamide, as when a solution of thiamine alone decomposed at pH 8. Both solutions containing these reducing substances, which indeed may have been the same, were capable of destroying cyanocobalamin. Ferric chloride added to the thiamine-niacinamide solution at pH 4.0-4.5 spared cyanocobalamin from reduction by the decomposition products. Stabilization of cyanocobalamin by ferric chloride also was noted in solutions prepared at pH 8 but was incomplete. A summary of these findings is given in Table 7.

TABLE 7

STABILIZATION OF VITAMIN B_{12} BY $FeCl_3$

	Niacinamide	$FeCl_3$	*Potency After Test*	
pH	*mg./ml.*	*mg./ml.*	B_1 *(mg./ml.)*	B_{12} *(mcg./ml.)*
4.0	——	——	11.0	4.5
8.0	——	——	7.5	0.5
8.0	——	0.5	6.2	2.5
4.0	100	——	10.6	nil
4.0	100	0.5	10.6	4.5
8.0	100	——	7.0	0.5
8.0	100	0.5	5.1	2.5

Ref.—Mukherjee & Sen, *J. Pharm. Pharmacol. 11,* 26 (1959).
Initial Conc.—Thiamine = 15 mg./ml.
Vitamin B_{12} = 5 mcg./ml.
Test—Heat at 100°C./4 hours.

The observations of the effect of thiamine and niacinamide on cyanocobalamin also were confirmed by Gambier and Rahn in Brazil (19). But these workers defined a critical ratio, a critical pH, and special conditions for processing the parenteral solutions which excluded heat. Stable solutions containing thiamine, niacinamide, and cyanocobalamin could be prepared by these special means if the thiamine-cyanocobalamin ratio did not exceed 120 to 1. If the thiamine-cyanocobalamin ratio was 5,000 to 1 or 10,000 to 1, then even the refined techniques failed to prevent decomposition of cyanocobalamin.

The problem of cyanocobalamin decomposition by thiamine is especially acute in high-potency parenteral products. It is much less likely to occur in maintenance-type oral liquids where concentrations invariably are smaller and where non-aqueous vehicle components contribute toward stabilization. Nevertheless, methods have been devised for minimizing the incompatibility in parenteral solutions and stable products are available commercially. One method which assures maximum stabilization involves lyophilization.

Thiamine and Riboflavin—An incompatibility between thiamine and riboflavin has been reported in aqueous B-complex solutions which manifests itself in physical changes involving trace precipitation of thiochrome or chloroflavin (20).

The precipitation of thiochrome is induced by the oxidative action of riboflavin on thiamine. It occurs more rapidly, the greater the riboflavin concentration. The presence of a greater quantity of air in the ampuls over the solutions also accelerates the process. On the other hand, the reducing action of thiamine or its decomposition products on riboflavin is denoted by the crystallization of chloroflavin. It occurs more readily as the ratio between thiamine and riboflavin concentrations increases. When the chloroflavin crystals in decomposed solutions are redissolved, full recovery of riboflavin potency is attained. The incompatibility has been reported to be completely eliminated in solutions containing thiamine, riboflavin, pyridoxine, and niacinamide by the addition of ascorbic acid (21).

Cyanocobalamin and Ascorbic Acid—The marked decomposition of vitamin B_{12} and vitamin B_{12} concentrates in aqueous solutions of ascorbate was first reported in 1949 by Gakenheimer and Feller (22). Subsequent studies showed that the rate of loss of cyanocobalamin in

ascorbate solution at pH 2.5 and 3.0 was approximately 1.5 per cent per day at room temperature. Vitamin B_{12a}, on the other hand, when examined under identical conditions, showed practically complete loss of color and activity within one day. The cyanocobalamin-ascorbate reaction was observed to progress faster at higher pH and was complete in less than one hour at pH 7 (23).

In another study, ascorbic acid was reported to be destructive for non-cyanocobalamins such as chloro-, nitro- and thiocyanatocobalamin, decomposition in pH 4 buffer requiring only a few hours at 25°C. Furthermore, the stability of vitamin B_{12} concentrates to ascorbate varied directly with their cyanocobalamin content (24).

In view of this prominent incompatibility and the desire on the part of manufacturers and clinicians alike to have both vitamins present in the same multivitamin formulation, a great deal of work has been done in recent years with an aim toward stabilizing the B_{12}-ascorbate reaction. Many totally-unrelated methods were developed for improving the stability of cyanocobalamin in the ascorbate system and in other compositions. These are generally described in patents. A brief review of some of these will be interesting.

Soluble, non-toxic bitartrate salts at a preferred concentration of 0.1% have been employed to stabilize vitamin B_{12} concentrates against destruction by heat (25). Thiodipropionic acid (0.1%) was also described for the same purpose (26). Reasonably stable solution compositions containing crystalline vitamin B_{12}, or a mixture of B_{12} and B_{12a} derived from concentrates, with ascorbic acid and thiamine were claimed to be produced by cooperating stabilizers which included Tween 20, cysteine HCl and sodium copper chlorophylline or the sodium salt of yeast nucleic acid (27). Ammonium sulfate (100-10,000 mcg. per ml.) has been employed to prepare storage-stable solutions of vitamin B_{12} concentrates which contained substantial proportions of hydroxocobalamin (28). To overcome destruction of B_{12} by ferrous salts, a composition containing ferric versenate was described (29). Resin adsorbates of vitamin B_{12} on cation exchangers were claimed to have unusual stability, especially under acid conditions in the presence of ascorbic acid, ferrous iron, and other reducing agents (30). More recently, α-hydroxynitriles (mandelonitrile) (31), non-toxic cationic salts of metallocyanide complexes (potassium ferrocyanide, potassium cobalticyanide) (32), non-toxic nitrites (33), and soluble molybdenum compounds (sodium or ammonium molyb-

date) (34), all have been claimed as stabilizing agents for the B_{12}-ascorbate decomposition.

However, perhaps the most significant method for improving the stability of these very troublesome cyanocobalamin systems arose from the observation of Skeggs (35), who found that the activity of aqueous solutions of vitamin B_{12} concentrates could be improved considerably by the addition of saccharated iron oxide. The idea of using soluble iron salts was successfully applied to the stabilization of aqueous solutions of cyanocobalamin and ascorbic acid by Newmark (36), wherein the non-toxic iron compound was added in the range of 17-1700 mcg. per ml. This low concentration of iron, surprisingly, did not appear to affect ascorbic acid stability and in many cases did, indeed, stabilize the cyanocobalamin component. Some data showing the stabilizing effect of saccharated iron oxide on the cyanocobalamin-ascorbate system are given in Table 8. This system now is used rather widely commercially for producing oral, liquid multivitamin products.

TABLE 8

STABILITY OF CYANOCOBALAMIN AND ASCORBIC ACID IN LIQUIDS WITH AND WITHOUT SACCHARATED IRON OXIDE (50 mcg./ml.)

	With Fe		*No Fe*	
	B_{12}	*C*	B_{12}	*C*
		Polyvitamin Drops		
Initial	100%	100%	100%	100%
50°C.-20 days	61%	62%	Trace	31%
37°C.- 1 month	100%	90%	Trace	97%
RT - 2 months	92%	95%	30%	97%
RT - 4 months	92%	89%	——	——
		Polyvitamin Syrup		
Initial	100%	100%	100%	100%
50°C.-10 days	92%	92%	Trace	80%
50°C.-30 days	59%	79%	Trace	45%
37°C.- 1 month	82%	93%	69%	96%
RT - 4 months	——	——	60%	94%

Another process for stabilizing the cyanocobalamin-ascorbate reaction employs a water-swellable clay of the Montmorillonite type (Veegum, Thix) (37).

Preliminary studies by Bartilucci suggested that the decomposition products of ascorbic acid were involved in the destruction of cyanocobalamin in aqueous solution (38). Later work provided evidence that increasing concentrations of dehydroascorbic acid produced progressively greater losses of cyanocobalamin in ascorbic acid solution (39).

Finally, commercial 70% sorbitol solution has been employed as a vehicle, alone or in mixture with glycerin, for oral liquid products containing ascorbic acid, cyanocobalamin, and ferrous gluconate. Circumvention of the mutual incompatibilities in such preparations even after prolonged storage at room temperature was attributed largely to the binding of water by sorbitol. The possible complexation between sorbitol and either or both ascorbic acid and cyanocobalamin also was suggested (40).

The studies of Barr *et al.* (41) showed that cyanocobalamin alone was stable in sorbitol and in glycerin, whereas dextrose and sucrose solutions caused decomposition during storage at 25°C. and 45°C. In this connection, Bartilucci (42) cautioned that sorbitol containing trace metal contaminants as a result of improper storage was destructive to ascorbic acid.

Miscellaneous—Two other interactions between vitamins are worth noting. The first is the canary-yellow "addition compound" that forms when equimolar quantities of ascorbic acid and niacinamide are mixed, especially in the dry state. This reaction product maintains essentially the full potency of each constituent but has a different melting point than either component. A patent issued to Fox and Opferman (43) teaches that, unless this compound is preformed, subsequent difficulty may arise with thickening and hardening of the mixtures employed in filling soft gelatin capsules.

The second interaction involves the incompatibility of folic acid in cyanocobalamin solutions adjusted to pH 6. At this pH, 5 mg. per ml. of folic acid is stable and remains in solution only if niacinamide also is added to maintain clarity and serve as a stabilizing component (44).

Finally, this paper would be incomplete without reference to the excellent studies of Garrett dealing with the prediction of stability of multivitamin products (45).

A great deal more could be said about methods of formulating multivitamin products, choice of granulating methods and coating

procedures in tablet manufacture, selection of solubilizers and vehicles for liquids, vitamin-mineral combinations, and many other topics. Despite the numerous problems, various ways have been devised for producing multivitamin and vitamin-containing combinations having acceptable stability in both solid and liquid form. Much of this is due to the ingenuity and resourcefulness of research pharmacists in searching out and developing techniques, solvents, derivatives, and stabilizing additives. Their efforts have contributed substantially toward the establishment of numerous stable and useful products currently available in world-wide markets.

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BOOK REVIEW

Heterocyclic Chemistry. A. R. Katritzky and J. M. Lagowski. 274 pp. John Wiley & Sons, Inc., New York, N. Y., 1960. Price: $4.75.

The authors have endeavored to construct a text on heterocyclic chemistry which is intended to indicate to the student that brute memory is not a prerequisite to the comprehension of heterocyclic syntheses. The approach to reaction sequences is wholly electronic in nature and should appeal to the educator and student with a leaning toward the modern concepts of organic chemistry.

The subject matter covers three through eight membered ring systems, with the emphasis on five and six membered compounds. Each chapter is subdivided to consider reactions of the heterocyclic and non-heterocyclic ring systems in the case of fused ring systems. A short chapter of ring systems involving atoms other than nitrogen, sulfur, or oxygen is also included.

For the most part, the nomenclature follows the *Chemical Abstracts* system with only slight reversion to European nomenclature.

From the pedagogic viewpoint, the lack of review questions and the meagre treatment of physical data, to perhaps correlate with electronic mechanistic interpretations, detracts somewhat from the usefulness of the book as an undergraduate text. Also, no doubt in the desire to be complete, the text includes a tremendous wealth of information and some topics are treated sketchily, a source of confusion even for the more advanced student.

It is refreshing, however, to see this new and logical approach to heterocyclic organic chemistry, and the authors must be commended for their organization and treatment of the subject in a rational manner. The text is highly recommended for the student and research worker desirous of emerging from the "cook-book" status of heterocyclic chemistry.

A. R. Gennaro

INDEX TO VOLUME 132 OF THE AMERICAN JOURNAL OF PHARMACY

AUTHOR INDEX, 1960

(B)—Book Review

(E)—Editorial

SUBJECT INDEX, 1960

(A)—Abstract
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(E)—Editorial

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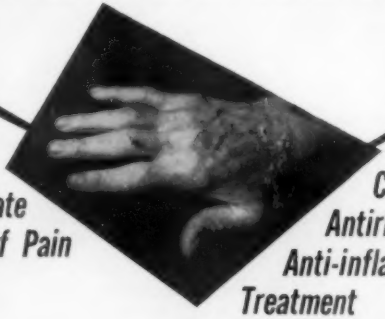

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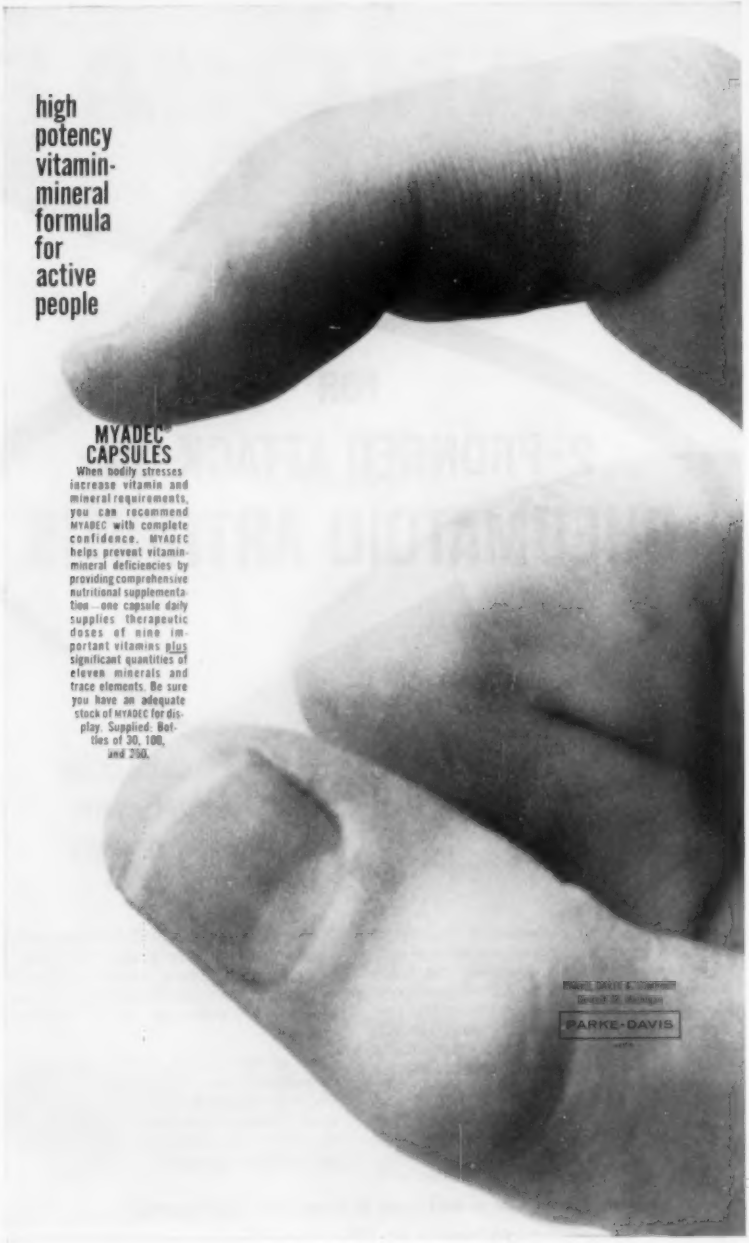
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American Journal of Pharmacy

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